Rationale and Design of ACT-EARLY, the Acoramidis Transthyretin Amyloidosis Prevention Trial

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BACKGROUND

- ATTR is a systemic, progressive, fatal disease. Dissociation of destabilized, tetrameric TTR into its constituent monomers facilitates misfolding, aggregation, and deposition as amyloid in the heart, peripheral nervous system, and other tissues. Destabilization is associated with aging (ATTRwt) and is accelerated by one of over 140 known pathogenic, destabilizing TTR gene variants (ATTRv)[1]
- ATTR-CM is an infiltrative, restrictive form of heart failure, typically presenting as HFpEF.[2] ATTR-PN is an ascending, axonal neuropathy of the sensorimotor and autonomic peripheral nervous system. The most common cause of death in ATTRv is end-stage heart failure, which occurs 10-15 years after diagnosis in ATTRv-PN and 3-5 years in ATTRv-CM[3,4]
- Several disease-modifying drugs have been approved for treating either ATTRv-CM or ATTRv-PN, depending on the predominant phenotype. None of these agents have been evaluated or approved for the prevention of ATTRv in asymptomatic carriers of a pathogenic TTR variant. Few guidelines have been agreed upon or established for their clinical surveillance[5]
- Acoramidis, a next-generation, near-complete TTR stabilizer, has recently completed and communicated the results of a pivotal phase 3 trial in patients with established ATTR-CM.[6] The study met its primary endpoint of a hierarchical analysis of all-cause mortality, cardiovascular hospitalization, NT-proBNP, and 6MWT (p<0.0001). The safety profile remains reassuring with no important safety signals of potential clinical concern identified to date
- The observation that intervention early in the natural history of ATTR is associated with greater clinical benefit[7-10] suggests a potential prophylactic role for acoramidis in appropriately selected at-risk individuals. The AG10-501 study is designed to test this hypothesis and will include patients with V30M/pV50M, V122I/pV142I, T60A/pT80A, and other pathogenic variants

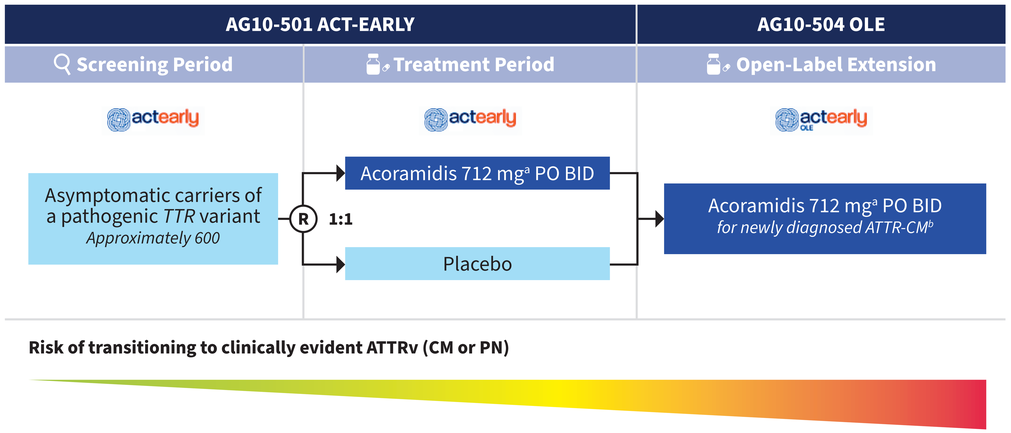
CONCLUSION

- **AG10-501 ACT-EARLY is the first phase 3 trial to evaluate prophylactic therapy for the prevention of ATTR. ACT-EARLY is also the first phase 3 clinical trial to consider ATTR not by traditional dichotomized cardiomyopathic or polyneuropathic manifestations, but as one disease anchored by a single fundamental pathobiology. Enrollment will begin in 2024**

METHODS

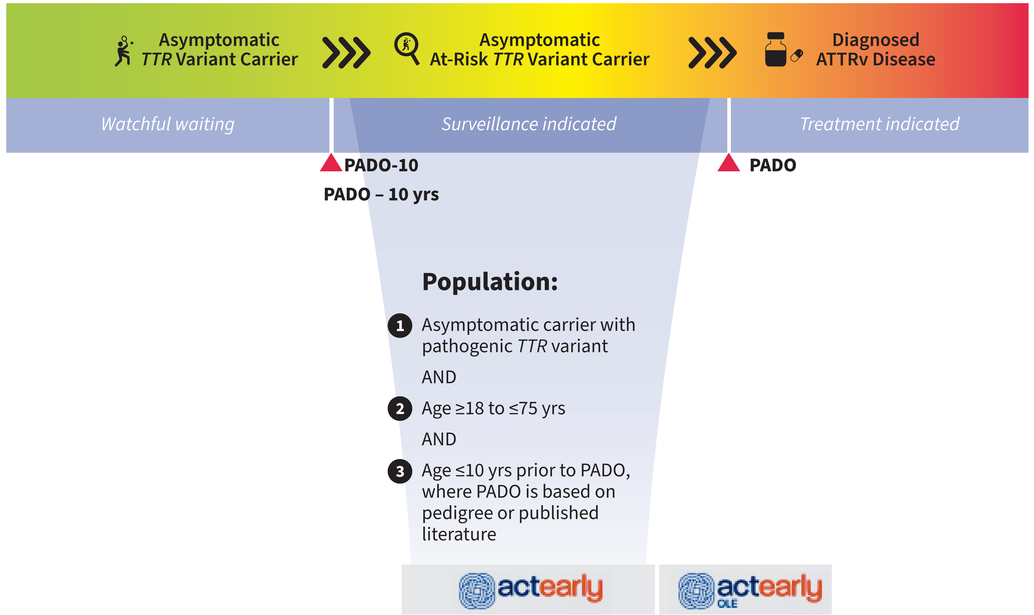
- ACT-EARLY is a prospective, multinational, randomized, double-blind, placebo-controlled study evaluating treatment with acoramidis in asymptomatic carriers of a pathogenic *TTR* variant (**Figure 1**). Eligible participants are individuals (age 18-75 years) with a known pathogenic *TTR* variant who are within 10 years of the predicted age of disease onset for their specific variant (**Figure 2**). Approximately 600 participants will be randomized 1:1 to receive acoramidis or placebo for up to 7 years. The primary efficacy endpoint is time to development of ATTR-CM and/or ATTR-PN. Additional endpoints include safety and tolerability of acoramidis, and its effects on cardiac imaging parameters, plasma TTR concentration, nerve conduction, and neurofilament light chain

FIGURE 1. AG10-501 ACT-EARLY and OLE Schematic. ACT-EARLY is a prospective, multinational, randomized, double-blind, placebo-controlled study evaluating treatment with acoramidis in asymptomatic carriers of a pathogenic TTR variant.



[a]Acoramidis 712 mg is the content of the moiety equivalent to the 800 mg acoramidis HCL dose used in the pivotal phase 3 ATTRibute-CM trial.
[b]Participants newly diagnosed with ATTR-PN should seek therapy with standard of care outside of this trial.

FIGURE 2. Current Care Paradigm as Risk of Clinically Evident ATTRv Increases in Carriers of a Pathogenic *TTR* Variant. The ideal recruitment window for AG10-501 relies on the predicted age of disease onset.



FUNDING: This study was sponsored by BridgeBio Pharma, Inc., San Francisco, CA, US.

ABBREVIATIONS: 6MWT, 6-minute walk test; ATTR, transthyretin amyloidosis; ATTR-CM, ATTR cardiomyopathy; ATTR-PN, ATTR polyneuropathy; ATTRv, ATTR variant; ATTRwt, ATTR wild-type; HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OLE, open-label extension; PADO, predicted age of disease onset QoL; R, randomization.

ACKNOWLEDGMENTS: Under the direction of the authors, medical writing assistance was provided by Syneos Health Medical Communications, LLC, and supported by BridgeBio Pharma, Inc. Editorial support and critical review provided by Shweta Rane of BridgeBio Pharma, Inc.

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